An update in the diagnosis and management of juvenile dermatomyositis

Juvenile dermatomyositis (JDM) is a rare pediatric rheumatic disease. It belongs to the group of idiopathic inflammatory myopathies of childhood. JDM is the most frequent of the idiopathic inflammatory myopathies (it represents 85% of cases) among children. JDM is classified by the Bohan and Peter criteria set in 1975. New criteria are being developed and newly developed diagnostic tools are being used in daily clinical practice. This review focuses on recent publications regarding the epidemiology, pathogenesis, classification and treatment of JDM, and will discuss some relevant publications from the adult myositis literature.

KEYWORDS: childhood dermatomyositis ■ children ■ dermatomyositis ■ juvenile dermatomyositis

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Idiopathic inflammatory myopathies (IIM) represent a group of autoimmune muscle conditions with variable organ involvement amongst the different types [1]. Juvenile dermatomyositis (JDM) is the most prevalent subgroup among children (accounting for up to 85% of cases), while polymyositis, inclusion body myositis and dermatomyositis are most common in adults [2]. JDM is primarily a capillary vasculopathy affecting the muscles and skin, but involvement of multiple organ systems have been reported. The course of JDM is variable. Approximately one-third of patients have a monocyclic disease course. This review will focus on classification and treatment of JDM.

Epidemiology

The incidence of JDM has been estimated at two to three per million children per year [3–5]. The average age at onset is 7 years old, however, approximately one-quarter of the patients are less than 4 years of age at diagnosis [2]. All groups of childhood IIM, including JDM, are more frequent in females [2,4–7]. The racial distribution reported in the US and UK national registries show a predominance of Caucasian children (65–83%), followed by African–American children (8–11.4%) [2,3].

Etiology & pathogenesis

The etiology of JDM is becoming better understood. A genetic predisposition is strongly suggested by the predisposition for certain HLA types in patients with JDM [8]. As well as HLA predisposition, the *TNF-α-308A* allele has been associated with increased disease severity, calcinosis, ulceration and duration of JDM [9,10]. In the Caucasian population, polymorphisms of the IL-1 receptor antagonist gene were found to be associated with an increased risk for JDM [11]. A recent study of plasma proteomic profiles in disease-discordant monozygotic twins suggest that disease pathology is likely influenced by post-meiotic genetic events (e.g., copy number variations between monozygotic twins), different epigenetic modifications, epistatic protein interactions, and/or environmental exposures that promote proinflammatory biologic pathways [12]. This indicates that proteomic profiles may play an important role in disease pathogenesis. An increased prevalence of autoimmune diseases (lupus and Type 1 diabetes) in families of children with JDM, suggest shared pathogenic factors [13].

Environmental triggers, such as infections [14,15], sun exposure, vaccines and medication, have been suggested in the pathogenesis of JDM. Several studies reported symptoms consistent with an infection prior to the development of JDM [14,15]. No consistent serological or tissue evidence of an infectious agent playing a direct role in the pathogenesis has been reported [16].

Both the humoral (autoantibodies and immune complexes) and cellular (T and B cells) components of the adaptive immune system are thought to contribute to the pathogenesis of JDM. Myositis-associated antibodies and myositis-specific autoantibodies (MSAs) have been reported to be positive in up to 40% of children with JDM and in up to 70% of adults with IIM [17,18]. With increasing knowledge of new autoantibodies this number may rise and may increase our understanding of the pathogenesis. A major mechanism of vessel damage in JDM is

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complement activation inducing further cytokine release and vessel injury via the membrane attack complex. JDM patients show an overexpression of MHC-I and β2-microglobulin in affected muscle tissue [19]. JDM patients also show a preference of expressing ICAM-1-type adhesion molecules in the affected muscle vessels, while adult dermatomyositis (DM) patients have a preference for VCAM-1 [20]. Tubuloreticular inclusion bodies are present in JDM and adult DM patients and have been reported in circulating blood cells of other patients treated with IFN-α and in cultured endothelium cells in response to treatment with interferons [21–23]. Tubuloreticular inclusion bodies likely indicate increased IFN pathway signaling [24].

There has been increasing evidence that the innate immune system also plays a role in JDM. In JDM, and other IIM types, the presence of T lymphocytes indicate an ongoing permanent immune response. This ongoing immune response requires the presence of dendritic cells. Dendritic cells are known to bridge the innate and adaptive immune responses [25]. Although the understanding of the pathogenesis of JDM has improved, more knowledge is needed to fully comprehend and associate the clinical features and initiate targeted treatment regimens.

Diagnostic criteria

The diagnosis of JDM is considered in a patient with a typical rash on the face or body and symmetrical muscle weakness. The 1975 criteria of Bohan and Peter are still the most widely used [26]. These criteria comprise: first, symmetrical weakness of the proximal muscles; second, characteristic cutaneous changes consisting of heliotrope discoloration of the eyelids, which may be accompanied by periorbital edema, and erythematous papules over the extensor surfaces of joints, including the dorsal aspects of the metacarpophalangeal and proximal interphalangeal joints, elbows, knees or ankles (Gottron papules); third, elevation of the serum level of one or more of the following skeletal muscle enzymes; creatine kinase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase and aldolase; fourth, electromyographic demonstration of the characteristics of muscle irritability and denervation; and fifth, muscle biopsy documenting histological evidence of myositis. The most typical histologic features of JDM are perifascicular atrophy, centralization of nuclei, degenerating fibers, regenerating fibers, and a scattered inflammatory infiltrate (often around vessels). Specialized staining will often show a decrease in the number of capillaries in the muscle, and on electron microscopy, tubuloreticular inclusions are often seen. The sensitivity and specificity of the Bohan and Peter criteria have never been validated for children; it is thought that individually they are probably 45–90% accurate [2]. According to the 1975 criteria, a definite diagnosis of JDM is considered when patients present with three criteria in addition to the rash, and a probable diagnosis is considered if a patient presents with two criteria in addition to the rash [26]. Electromyography and muscle biopsy are both invasive tests and have slowly been replaced by the noninvasive muscle MRI at many centers, especially in patients with a classic rash and proximal symmetrical muscle weakness. MRI findings suggestive for muscle inflammation include symmetrical muscle edema in the thigh muscle on fat-suppressed T_2-weighted or short tau inversion recovery sequences. An international survey in 2006 of 92 centers from 32 countries showed that currently, 70% of the centers have access to muscle MRI and only 61 and 55% used muscle biopsy and electromyography in the investigation of children with suspected myositis, respectively [27]. Muscle MRI has been used more often and clinical scoring systems are being developed [28–31]. These scoring system are acceptable for the single reader, but there is more variability between readers [28]. In a study with 102 patients with childhood myositis, 78 patients had MRI abnormalities consistent with myositis [2]. A recent study showed no correlation between the severity of the MRI findings of muscle or fascia with the clinical outcome in patients with newly diagnosed JDM, however, an abnormal subcutaneous fat signal appears to have a significant association with a more aggressive chronic disease course [32]. These new tests and data suggest the need for new diagnostic criteria based on modern methods of diagnosis. Another test that should be considered in the new diagnostic criteria is nailfold capillaroscopy, which shows a high correlation with disease activity and recovery during follow-up [33].

Clinical manifestations

The clinical manifestations of JDM can be quite diverse. In larger series the most common, extramuscular clinical manifestations are cutaneous (80–90%), arthritis (25%), constitutional features (16–18%), pulmonary involvement (11%) and gastrointestinal involvement (5%) [2,7].

Constitutional features

Fever, anorexia and adenopathy are seen in 10–15% of JDM patients. A recent study looking

at sleep and fatigue and the relationship with pain in patients with JDM and juvenile idiopathic arthritis reported increased pain and decreased quality of life in patients with sleep disturbances and fatigue [34]. Sleep disturbance and fatigue were present in almost half of the patients with JDM, suggesting that better strategies aimed at improving sleep and fatigue might improve the quality of life in these patients [34].

Musculoskeletal manifestations

One of the hallmarks of JDM is symmetrical muscle weakness. Muscle weakness is most often present in all muscle groups but is most obvious in the limb-girdle musculature, the anterior neck flexors, and the trunk muscles. Findings on physical examination may include the Gower's sign and the Trendelenburg sign. These tests can be challenging in very young patients. Affected muscles may, on occasion, be tender, edematous or indurated. Dysphagia and dysphonia are manifestations of weakness of the palatal and pharyngeal muscles and may be a risk for aspiration and regurgitation of liquid through the nose. Arthralgia and arthritis are frequently present during the JDM disease course [7,35]. The arthritis is usually nondestructive and nondeforming. Arthritis is often seen in the beginning of the disease course and frequently involves the knees, but large and small polyarthritis with tenosynovitis can also been seen [7,35].

Dermatological manifestations

Cutaneous manifestations are often the first to appear, or become present with or just after the onset of muscle symptoms [2]. JDM can present with several different rashes, but only two rashes are pathognomonic; Gottron's papules and heliotrope rash over the eyelids [36]. In 80% of patients, a pathognomonic rash is present at presentation; in the remainder, a less characteristic rash occurs [5]. The three most typical cutaneous manifestations are heliotrope discoloration of the upper eyelids, Gottron's papules, and periungual erythema with capillary loop abnormalities [36,37]. The heliotrope rash classically occurs over the upper eyelids and has a violaceous, or reddish purple tint. The heliotrope is often accompanied by edema of eyelids and face and eyelid capillary telangiectasia [38]. Patients with eyelid rash often also have a facial rash that may mimic the malar rash seen in systemic lupus erythematosus. Gottron's papules are papulosquamous areas of skin with a red appearance and are especially common over the extensor surfaces of the proximal interphalangeal, metacarpophalangeal and distal interphalangeal joints of the hands. The extensor surface of the elbows, knees, and the medial malleoli are less frequently involved; the toes are rarely affected. Nailfold capillary changes may be observed in clinic using a water-based gel and a magnifying glass (e.g., otoscope or ophthalmoscope) or a DermLite®. Characteristic nailfold capillary features of JDM include capillary dilatation, tortuosity, hemorrhage and drop-out. Nailfold capillary density appears to be a marker of skin and muscle disease activity, and can be an important marker of disease activity and recovery during patient followup [33,39]. Reduced nailfold density should be considered for inclusion as a diagnostic criteria as it has a high sensitivity.

Gingival capillary changes are also observed in patients with JDM. A unique gingival pattern characterized by erythema, capillary dilatation and bush-loop formation was observed only in JDM patients (61% compared with 0% in healthy controls) [40]. This might indicate that recognition of gingival telangiectases and capillary changes as an important diagnostic marker of JDM, which could lead to an earlier diagnosis [40,41].

Ulcerative cutaneous manifestations are serious and potentially life-threatening (in that they often indicate serious internal organ involvement) in JDM. Ulceration reflects significant vasculopathy in the skin with tissue hypoxia and necrosis. A severe course with a higher likelihood of a poorer outcome and persistent weakness are associated with ulcerations of the skin.

Calcinosis usually develops within a few years of diagnosis and is hypothesized to develop through a dystrophic mechanism, whereby involved muscle releases mitochondrial calcium into matrix vesicles, which then promotes mineralization [42]. Dystrophic calcinosis occurs in approximately one-third (12–43%) of children during the disease course and is less frequently present at diagnosis (3–23%) [2,7,43]. Calcium deposits may occur in subcutaneous plaques or nodules (usually on the extremities), as deep large tumorous deposits in muscle groups, as calcifications within fascial planes, bridging joints, or as an extensive subcutaneous exoskeleton [44,45]. Risk factors for calcinosis include delay to diagnosis and a longer duration of untreated disease, longer duration of active disease, inadequate treatment, underlying cardiac or pulmonary disease and the need for aggressive second-line immunosuppressive treatment [44,46]. Calcinosis can lead to complications,

including joint contractures, localized pain, inflammatory reactions (which may be indistinguishable from cellulitis or abscess) and uncommonly patients can develop an exoskeleton of calcinosis.

Cardiopulmonary disease

Cardiovascular complications in JDM are thought to be rare. Nonspecific sinus tachycardia is sometimes reported, and murmurs and cardiomegaly with or without ECG abnormalities have also been reported [7,46]. A recent study comparing the cardiac function of JDM patients with matched controls from the population, showed subclinical left ventricular diastolic dysfunction only in the JDM patients (22% compared with 0%) [47]. Findings of this study do suggest subclinical heart disease related to the systemic nature of JDM. A study of adults 29 years after onset of JDM showed an increased intima media thickness, impairment of endothelial cell function was measured by brachial arterial reactivity, and higher systolic and diastolic blood pressure than healthy controls [48]. These adult patients had continued active JDM. In adult polymyositis and DM interstitial lung disease is a frequent complication and is associated with high morbidity [49,50]. Data regarding pulmonary involvement in JDM are sparse. Asymptomatic pulmonary impairment was found in five out of 12 patients with JDM in a longitudinal study [51]. Recently Sanner *et al.* showed smaller lung volumes in JDM patients compared with controls, with a restrictive ventilatory defect in 26% and high-resolution CT abnormalities in 37% [52]. Again the high frequency of mostly subclinical pulmonary involvement highlights the systemic nature of JDM.

Gastrointestinal involvement

The GI tract can be involved in JDM, therefore monitoring for signs and symptoms of GI vasculopathy is necessary. GI vasculopathy can occasionally lead to bowel ischemia, necrosis, ulcerations and perforation [53,54]. Malabsorption with decreased absorption of nutrients and, most notably, oral prednisone has been described [55].

Lipodystrophy

Acquired lipodystrophy is being increasingly recognized in patients with JDM. These changes are rarely seen at presentation, but develop later in the course of the disease in 14–25% of patients [7,56]. Lipodystrophy is characterized by a progressive, slow and symmetrical loss of subcutaneous fatty tissue that mainly involves the upper body [56].

Treatment

No prospective, double-blind, randomized studies of immunosuppressive therapy in JDM have been completed. After the introduction of corticosteroids, the mortality was reduced markedly compared with historical controls. A team approach and general supportive care, including individualized physiotherapy in combination with drug therapy are essential. Treatment regimens are based on observational studies, expert opinions and clinical experience. A JDM treatment survey amongst pediatric rheumatologists in North America reported the use of corticosteroids in combination with another immunosuppressive agent (mostly methotrexate [MTX]) by almost all responders [57]. The dose and administration route of corticosteroids varied widely amongst responders. Consequently the Childhood Arthritis and Rheumatology Research Alliance developed three consensus treatment protocols that reflect current initial treatment of children with moderately severe JDM [58]. These protocols are combinations of intravenous methylprednisolone (IVMP; pulses for 3 days), MTX, oral prednisone and intravenous immunoglobulin (IVIG). Using these protocols, a comparison of different approaches to the treatment of JDM in North America is possible. This will enhance future understanding of the optimal treatment approach. A recent international multicenter study demonstrated that patients with recent-onset JDM were more likely to show significant clinical improvement (up to 90%), when compared with patients treated for a disease flare over a 24-month period. Differences in initial treatment were observed among the four geographical areas analyzed [59].

Corticosteroids are usually initiated as the onset of action is rapid, and treatment usually allows early control of the disease process. The clinical efficacy of corticosteroids can be seen within days to weeks. If patients receive high-dose corticosteroids (2 mg/kg/day) within the first 4 months of disease onset, better functional outcome and less calcinosis is seen than in patients treated with lower doses or later in the disease course [44]. Corticosteroid treatment may lead to troublesome side effects, including growth retardation, Cushingoid appearance, elevation of blood pressure, cataracts, vertebral fractures and osteoporosis. At The Hospital For

Sick Children (Toronto, Canada) patients are treated initially with 2 mg/kg/day of prednisone divided into three doses. After 6 weeks, if clinical improvement is seen, prednisone is consolidated to twice daily and shortly afterwards to once-daily dosing. As long as the disease stays clinically controlled, prednisone is tapered by approximately 10% every 2 weeks [60]. If GI vasculopathy, dysphagia, dysphonia or pulmonary disease is present, the initial treatment is usually IVMP (30 mg/kg/day, with a maximum of 1 g). Many surveyed rheumatologists prefer IVMP over oral prednisone on a routine basis (see above) [57]. A comparative study did not find a difference in 3-year outcomes between patients treated with IVMP and oral prednisone; the most severe patients, however, were all treated with IVMP and could not be matched [61]. In cases of incomplete or absent response, IVMP is often given with the assumption that oral corticosteroids are not being properly absorbed [55].

MTX is prescribed as a corticosteroid-sparing agent for many rheumatologic conditions. A shorter average time to discontinuation of prednisone and a lower average cumulative prednisone dose was reported in newly diagnosed JDM patients treated with MTX (15 mg/m^2/week) and prednisone (2 mg/kg/day) compared with historical controls [60]. Currently MTX is widely used at the start of treatment as a steroid-sparing agent [58]. Low-dose MTX has also been reported in the treatment of DM skin disease [62]. IVIG has been used as an adjunctive treatment, typically for two groups of JDM patients: corticosteroid-resistant patients who do not respond adequately to corticosteroids early in the disease course, and corticosteroid-dependent patients who respond initially but are unable to be weaned off steroid therapy. The efficacy of IVIG was first proven in a trial of adult DM patients [63]. After three monthly infusions, strength, neuromuscular symptoms, skin rash and histopathological findings all improved. Recently Lam *et al*. reported the efficacy of IVIG in 78 JDM patients, especially in patients with steroid resistant disease [64]. Although patients treated with IVIG achieved quiescence later than controls in the unadjusted analysis, an effect was noted after the applied bias reduction methods; corticosteroid-resistant patients, especially, showed marked improvement over a prolonged follow-up. At our institution, IVIG (2 g/kg/dose, maximum 70 g) is administered as a single infusion every 2 weeks for the first five doses, and then generally administered on a monthly basis for up to 2 years. IVIG treatment is sometimes added months into the disease if patients experience steroid resistance or dependence. In severe cases, IVIG is used earlier in the disease course.

Another widely used steroid-sparing agent is cyclosporine, which appears effective in clinical practice; however, evidence is sparse. A recent PRINTO study reported use of cyclosporine in patients with a disease flare [59]. PRINTO is currently conducting an international, multicenter randomized trial to compare initial treatment with corticosteroids with treatment with corticosteroids and MTX or cyclosporine. In our experience, cyclosporine seems to be effective but treatment is often complicated by hypertension and hirsutism.

Mycophenolate mofetil has also been used in patients with JDM [65,66]. In a recent study, 50 JDM patients were treated with mycophenolate mofetil and showed decreased skin and muscle disease activity. Mycophenolate mofetil was steroid sparing and was well tolerated [66].

Cyclophosphamide has been used in severe cases, usually refractory disease complicated with severe pulmonary involvement, ulcerative skin disease or GI vasculopathy. In a study of 12 patients receiving monthly cyclophosphamide pulses, ten showed clinical improvement after 6 months, without serious side effects, and two died shortly after treatment was initiated [67]. In most centers, including ours, cyclophosphamide is reserved for patients with severe refractory disease or life-threatening organ involvement.

The use of infliximab, an anti-TNF-α monoclonal antibody has been described in five patients with refractory JDM with reported clinical improvement [68]. In adults with DM, however, no sustained benefit has been shown. The efficacy of rituximab, anti-CD20, was suggested in four JDM patients [69]. Recently the French Autoimmunity and Rituximab Registry reported on their small series of nine JDM patients treated with rituximab. Rituximab may be effective for treating muscle and skin involvement in a small subset of JDM patients with refractory disease, with a satisfactory safety profile [70]. However, studies in adult DM have been conflicting regarding the efficacy of anti-CD20 treatment for DM, and a recent randomized placebo phase trial, including patients with JDM, DM and polymyositis was not able to prove a benefit [71]. Further studies into efficacy and safety of rituximab in JDM are necessary before firm conclusions can be made.

Other immunosuppressive agents that have been used for disease control include hydroxychlorquine and tacrolimus [72–75].

Course of disease & outcome

As discussed above, the outcome of JDM before corticosteroid therapy was introduced was poor. After the introduction, the mortality rate dropped below 10% and functional outcome has improved markedly. As previously discussed, delayed diagnosis and treatment appears to lead to poorer outcome and more calcinosis [44]. The course of JDM can be variable and is divided into monocyclic, chronic continuous or polycyclic disease. Monocyclic disease occurs in approximately one-third of the patients and permanent disease remission occurs within 2–3 years after onset [76]. Patients with a monocyclic disease course often have a good response to standard treatment. The remaining two-thirds of the patients have a chronic continuous disease course, which may include periods of medication-controlled quiescence and periods of flare [76]. In a Canadian cohort, 37% of patients had a monocyclic disease, and the remainder of patients had a chronic disease course; polycyclic disease (in which there is medication-free remission followed by relapse) is distinctly unusual [76]. None of these patients reported interference of the disease in their ability to work. The median time to remission in this cohort was 4.67 years. The presence of a persistent rash at 3 months was a predictor for a poorer outcome [76]. In a recent long-term follow-up study of 490 patients with JDM, monocyclic disease was reported in 41% of the patients and chronic polycyclic or continuous in 58.7% [46]. Poor outcome predictors included either a polycyclic or continuous disease course. Severe impairment was seen in less than 10% of the patients, however, 40.7% of the patients had decreased functional outcome. The mortality rate was 3.1% [46]. In a cross-sectional follow-up study by Mathiesen *et al.* a disease duration of >4 years increased the risk of damage (predominantly cutaneous scarring 39.6% and muscle dysfunction 34%); disease onset age >7.4 years increased the risk of more than two affected organs, and disease duration of >4 years increased the risk of calcinosis and continuous muscle dysfunction [77]. The median disease duration was 13.9 years in this group of 53 patients. A case–control study including 59 JDM patients examined a median of 16.8 years after disease onset were compared with 59 age- and sex-matched controls [52]. JDM patients were weaker than controls based on muscle weakness/reduced endurance in 31–42% of patients and MRI detected muscular damage in 52% of patients. Active disease and muscle damage present 1-year postdiagnosis were predictors for poorer outcome.

Conclusion

In the past decade important steps have been made in the understanding of the pathogenesis and the treatment of childhood DM. Large international multicenter collaborations have been initiated and consensus treatment protocols are now available for use in daily clinical practice. These collaborations and protocols are necessary to get an even better understanding of the pathogenesis and to develop prediction models to tailor future treatment. Although outcome has improved drastically compared with historic controls, a large number of patients still experience impairment years after disease onset.

Future perspective

Increased understanding of environmental risk factors, genetic susceptibility and pathogenesis will lead to better understanding of the disease. This will lead to more tailored treatment options and better long-term outcomes.

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Executive summary

- Incidence of juvenile dermatomyositis is two to three per million children per year.
- Postmeiotic genetic events, different epigenetic modification, epistatic protein interactions and environmental exposure influences the disease pathology.
- Revised diagnostic criteria should include the use of muscle MRI and nailfold capillaroscopy.
- Treatment consensuses have been developed for juvenile dermatomyositis.
- Functional impairment is present in 50% of juvenile dermatomyositis patients years after disease onset.

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